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## **REMARKS**

### **Status of the Claims**

Claims 34-42 and 62-76 are pending herein.

Support for the amendment of claims 34, 37 and 39 can be found throughout the instant specification. See, for example, the Title, Technical Field, paragraph [0011], paragraph [0066], etc.

Support for the detergents of claims 71 and 73 can be found, for example, in paragraphs [0038] and [0085].

Support for the macromolecules of claims 72 and 74-76 can be found, for example, in paragraphs [0013] and [0040].

No new matter is added.

### **Claim Rejection under 35 U.S.C. 103-Levy in view of Paliard**

Claims 34-44 and 58-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,395,253 to Levy et al. (Levy) in view of US 6,562,346 to Paliard et al. (Paliard). Applicant respectfully traverses this rejection and its supporting remarks.

Among other requirements, to establish a *prima facie* case of obviousness, the prior art reference (or references) must teach or suggest all the claim limitations. See, e.g., MPEP 706.02(j) and the cases cited therein. Levy and Paliard do not meet this threshold.

As presently amended, all claims require processes whereby macromolecules are adsorbed to the microparticles. Levy, on the other hand, does not teach or suggest adsorption to microparticles, but rather is directed to improved methods for incorporating nucleic acids *into* polymeric microspheres and/or nanospheres (micro-encapsulation) through the use of a condensing agent. See, e.g., Abstract, Field of the Invention, etc.

Moreover, as explained in the present application at paragraph [0011] onwards:

The present inventors have found that adsorption of macromolecules to microparticles can be improved by ensuring that detergent is made available for forming a complex with the macromolecules at the time of adsorption. This availability can be accomplished, for example, by separately providing a quantity of detergent at the time of macromolecule adsorption or by ensuring that the process for producing the microparticles results in a product containing a substantial amount of unbound detergent.

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Thus, the application teaches two different approaches for ensuring that unbound detergent is available for forming a complex with the macromolecules at the time of adsorption, one of which involves ensuring that the process for producing the microparticles results in a product containing a substantial amount of unbound detergent.

In this regard, the claims in the present application require (I) that the microparticles are subjected to a filtration step such that a particular percentage (i.e., about 10-90%, 10-60% or 25-40%) of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound, (II) that the microparticles are not subjected to a washing step and the ratio of the detergent to the polymer used is such that a particular percentage (i.e., about 10-90%, 10-60% or 25-40%) of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound.

With respect to limitation (II) above, the Examiner argues that while the Examples of Levy require a washing step, other portions of Levy do not. Applicant has noted that, even assuming that portions of Levy do not require a washing step, one of ordinary skill in the art upon reviewing Levy would follow Levy's procedures, as set forth in the Examples, to produce microspheres. In particular, the Examples of Levy teach a method of producing microspheres comprising forming a W/O/W emulsion, evaporating the organic solvent from the W/O/W emulsion, recovering microspheres by ultracentrifugation, and washing recovered microspheres multiple times. See, e.g., the Examples of Levy. See also MPEP 2141.02.VI: A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

As noted in paragraph [0011] of the specification, techniques in which microparticles are washed multiple times with water, such as the process of Levy, remove essentially all unbound detergent, resulting in a final product in which greater than 99% of the remaining detergent is bound to the particles.

Moreover, Applicant is claiming the absence of a washing step in a method where the ratio of the detergent to the polymer used is such that a *particular percentage* of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound.

Nothing anything like this is disclosed in Levy. Levy does not describe compositions with bound and unbound detergent, much less in the amounts claimed for purposes of enhancing absorption.

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In this regard, the Examiner urges that "Levy does not categorically state that the microspheres produced are free of detergents and furthermore, Levy in one of the embodiments (col. 12, lines 58-67) does not employ a washing step." The Examiner further urges that "Levy does not state that the microspheres/particles formed are free of detergent; and it flows from one of the embodiment[s] that does not use a wash step but evaporates off the organic solvent ... that the detergent is not removed and as such, the microparticles would have detergent associated."

Applicant respectfully disagrees. First, it is noted that the solvent evaporation step referred to by the Examiner is not an *alternative* to washing, as appears to be suggested by the Examiner, but rather is a process that is used to yield solid microparticles from a dispersed oil phase (i.e., one containing polymer and solvent) in a W/O/W emulsion. (When the solvent is evaporated solid polymer particles are left behind.)

Moreover, absent a reason to ensure that unbound detergent remains in the microparticles, one of ordinary would be motivated to wash the microparticles of excess detergent by centrifugation as taught by Levy. Indeed, as indicated in Singh et al., *Proc. Natl. Acad. Sci. USA*, 2000, 97:811-816 (of record—see the IDS filed 2/10/04), page 815, right column, third paragraph, there is motivation in the art to keep detergent levels, particularly cationic detergent levels, to a minimum.

Furthermore, even assuming for the sake of argument that Levy does not require a washing step, the absence of a washing step still would not necessarily produce the particular amounts of bound and unbound detergent claimed. In this regard, see MPEP 2112.IV (emphasis in original)(citations omitted):

The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic...."To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' "....

The Examiner has not met this burden with respect to the amounts of bound and unbound detergent in Levy.<sup>1</sup>

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<sup>1</sup> With respect to the Examiner's statement that the claims do not recite the amount of detergent added to make the microparticle in the emulsion, it is noted that this amount would be understood by one of ordinary skill in the art to be whatever amount is required, in the absence of a washing step or in the presence of a filtration step, to achieve a composition which contains the amounts of bound and unbound detergent claimed.

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With regard to limitation (I) above (i.e., a step in which the microparticles are subjected to a filtration step such that a particular percentage of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound), it is first noted that Levy does not teach a filtration step.

The Examiner had previously taken the position that "centrifugation can be considered filtration." The Examiner subsequently agreed that "centrifugation is not a filtration" but urged that "filtration that collects particles or solids accomplishes [approximates?] the collection of particles or solid by centrifugation and the removal of unwanted components soluble and present in the solvent. The Hawley's Condensed Dictionary entry previously cited by Applicant describes "filtration" as "[t]he operation of separating suspended solids from a liquid (or gas) by forcing the mixture through a porous barrier ..." Because filtration requires the use of a porous barrier (i.e., a filter), filtration is neither taught nor suggested by Levy. As noted above, among other requirements, to establish a *prima facie* case of obviousness, the prior art references must teach or suggest all the limitations of the claims.

Moreover, as noted above, the claimed amounts of bound and unbound detergent are neither taught nor suggested (inherently or otherwise) by Levy.<sup>2</sup>

In summary, Levy neither teaches nor suggests the following: a method requiring macromolecule adsorption (all pending claims), a method requiring limitation I (see claims 36-38, 58, 59, 64, 65), a method requiring limitation II (see claims 39, 40, 60, 61, 66-69), or a method requiring limitation I or II (see claims 34, 35, 41, 43, 44, 62, 63, 70).

With respect to the cross-flow filtration as claimed in claim 36, the Examiner argues that because water is used to remove detergent in the cross-flow filtration process, this appears to be "equivalent to" washing, so the cross-flow filtration step of claim 34 "reads on" the wash step of Levy. However, the washing steps of Levy (which are performed in conjunction with centrifugation) have nothing to with filtration, which as noted above involves the use of a porous barrier (i.e., a filter) to separate suspended solids from a fluid (liquid or gas), much less cross-flow filtration as claimed.

With regard to SDS (an anionic detergent), it is true that Levy discloses 0.1% SDS in Section 5.3.2. However, Levy's use of SDS occurred *after* formation of DNA containing microspheres. In

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<sup>2</sup> In addition to ensuring that unbound detergent is made available for complex formation with macromolecules, the processes of the present invention are advantageous relative to those of Levy, *inter alia*, because they do not require a centrifugation step. This is extremely unwieldy from a manufacturing standpoint. By avoiding the need for a centrifugation step, the manufacturing process is greatly simplified, allowing for efficient scale up and for continuous manufacturing processing, as desired.

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particular, at column 19, lines 8-10, Levy specifically teaches incubating DNA-containing microspheres in excess TE buffer with and without 0.1% SDS. At column 19, lines 11-13, Levy discloses that SDS was used to establish that charge-related associations between poly-L-lysine and DNA contribute to the DNA release and/or extraction mechanism. Thus, in Section 5.3.2, the SDS is used as an *analytical reagent* to assess previously formed microspheres.

With respect to Paliard, this reference is cited for its disclosure of CTAB detergent, claimed in claims 38 and 40. Paliard, however, does not make up for the above noted deficiencies in Levy. For example, as elsewhere in the art at the time of the invention, Paliard teaches washing in Example 5 (see col. 23, lines 53-55). "The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness." MPEP 2145.X.D.3. Citing *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986).

Furthermore, because the SDS was used as an analytical reagent in Levy as noted above, the Examiner's assertion that it would have been obvious to use the CTAB of Paliard in place of the SDS of Levy is not persuasive.

Again, note that it is not at all obvious to retain detergent in unbound form as claimed. As indicated in Singh et al. *supra* (page 815, right column, third paragraph) there is strong incentive to keep the detergent levels to a minimum (e.g., by a method such as centrifugation with washing).

For at least the above reasons, it is respectfully submitted that the cited references do not support a *prima facie* case of obviousness against claims 34-44 and 58-67.

Reconsideration and withdrawal of the rejection of the claims under U.S.C. 103(a) as unpatentable over Levy in view of Paliard are respectfully requested.

#### **Claim Rejection under 35 U.S.C. 103-O'Hagan**

Claims 34, 35, 36, 42 and 43 are rejected under 35 U.S.C. 103(a) as unpatentable over US 6,086,901 to O'Hagan et al. (O'Hagan). Applicant respectfully traverses this rejection and its supporting remarks.

As noted above, each of the claims in the present application requires (I) that the microparticles are subjected to a filtration step such that about 10-90% of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound and/or (II) that the microparticles are not subjected to a washing step and the ratio of the detergent to the polymer used is such that about 10-90% of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound. Among the claims rejected in view of O'Hagan, claim

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36 is directed to a method requiring limitation I, claims 34, 35 and 43 are directed to methods requiring limitation I or II, and claim 42 is a product by process claim based on claim 34.

With respect to limitation (II), O'Hagan describes washing and centrifugation. See, for instance, Example 1, col. 14, lines 62-63 (washed three times using centrifugation) and Example 3, col. 16, lines 3-4 (also washed three times using centrifugation). This is noted by the Examiner, who urges that "there is no demonstration in applicant's specification that not subjecting the microparticles to a washing step provides unusual/unexpected results to the microparticles." Unexpected results, of course, can be used to overcome a *prima facie* case of obviousness. See, e.g., MPEP 716.02(a)-(g). Here, however, a *prima facie* case has not been made out. In particular, O'Hagan neither teaches nor suggests a process in which microparticles are not subjected to a washing step.

Moreover, as noted in paragraph [0011] of the present specification, techniques in which microparticles are washed multiple times with water, such as the process of O'Hagan, remove essentially all unbound detergent, resulting in a final product in which greater than 99% of the remaining detergent is bound to the particles. Thus O'Hagan further does not teach or suggest a process that produces the amount of bound and unbound detergent claimed.

With respect to limitation (I), O'Hagan does not teach or suggest a filtration step at all, much less one that would provide bound and unbound detergent in the amounts claimed.

This is even more clearly apparent with respect to the cross-flow filtration step claimed in claim 36. In this regard, the Examiner argues that the process of claim 36 "reads on washing because in the cross-flow filtration process, 4 liters of deionized water (Example 5) are used and the removal of the water appears to approximate the process of filtration/washing." As with Levy, however, the washing steps of O'Hagan (which are performed in conjunction with centrifugation) have nothing to do with filtration, which as noted above involves the use of porous barrier (i.e., a filter) to separate suspended solids from a liquid. Claim 36 is even more remote from O'Hagan, because it involves a particular type of filtration.

The Examiner correctly notes that claim 42 is a product by process claim. Nonetheless, claim 42 is unobvious over O'Hagan, because O'Hagan neither teaches nor suggests a method which produces the amounts of bound and unbound detergent claimed.

As noted above, it is not at all obvious to retain detergent in unbound form as claimed. As indicated in Singh et al. *supra* there is strong incentive to keep the detergent levels to a minimum (e.g., by a method such as centrifugation with washing).

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For at least the above reasons, it is respectfully submitted that O'Hagan does not support a *prima facie* case of obviousness against claims 34-36, 42 and 43. Reconsideration and withdrawal of the rejection of these claims over O'Hagan are respectfully requested.

### CONCLUSION

Applicants submit that the claims of the present invention are in condition for allowance, early notification of which is earnestly solicited. Should the Examiner be of the view that an interview would expedite consideration of this Amendment or of the application at large, request is made that the Examiner telephone the Applicant's attorney at (703) 433-0510 to resolve any outstanding issues.

### FEES

The Office is authorized to charge the one-month extension fee (\$120) and any additional fees required to deposit account number 50-1047.

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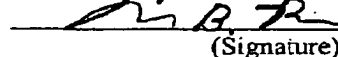
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